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Award Number: W81XWH-09-1-0746

TITLE: A Randomized Clinical Trial of Allopregnanolone for the Treatment of Severe Traumatic Brain Injury

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REPORT DATE: October 2013

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

☒ Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
October 2013	Annual	30September2012–29September2013

4. TITLE AND SUBTITLE
A Randomized Clinical Trial of Allopregnanolone for the Treatment of Severe Traumatic Brain Injury

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-09-1-0746

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of California, Davis

Davis, California 95618-6134

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSORING/MONITORING AGENCY REPORT NUMBER

12. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT
There is strong experimental support for the concept that allopregnanolone will be safe and have beneficial effects on disability when administered as a treatment following acute traumatic brain injury (TBI). This study will provide initial data on the safety and effectiveness of allopregnanolone in improving neurobehavioral outcome and reducing mortality in adults with moderate and severe TBI. A Phase 2, adaptive, two-stage, placebo controlled, double blind, randomized clinical trial is being conducted at the UC Davis Medical Center, a Level 1 trauma center, and at additional medical centers with appropriate expertise. Allopregnanolone has been manufactured GMP for this trial. Intravenous product solutions have been developed. Subjects are being allocated to 3 dosing levels (1) placebo, (2) low (50 nM), and (3) high (150 nM) by an innovative adaptive trial design consisting of two stages, in which safety and pharmacokinetics will be assessed in the first stage and adaptive allocation to the low and high doses will occur in the second stage. Key research accomplishments during the reporting period include: (1) Actively recruiting subjects; (2) No adverse safety signals in subjects treated to date; (3) Outcome data being collected; (4) Finalizing contracts with external sites to accelerate recruitment.

15. SUBJECT TERMS
traumatic brain injury, clinical trial, allopregnanolone

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES 9	19a. NAME OF RESPONSIBLE PERSON
			UU		USARMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPONE NUMBER (*Include area code)*
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Section I – Introduction

This study is intended to provide initial data on the safety and effectiveness of allopregnanolone in improving neurobehavioral outcome and reducing mortality in adults with moderate and severe traumatic brain injury (TBI). There is strong experimental support for the concept that allopregnanolone will have beneficial effects in TBI. Allopregnanolone, a neurosteroid that acts as a powerful modulator of $GABA_A$ receptors, has anticonvulsant and anesthetic activity but is free of the hormonal actions of progesterone (Rogawski and Reddy, 2004), another agent currently being studied in the treatment of TBI. Recent studies have demonstrated that allopregnanolone is efficacious in enhancing neurobehavioral recovery and decreasing TBI-induced neuronal death (Djebaili et al., 2004; 2005; He et al., 2004ab; Ciriza et al., 2006; Sayeed et al., 2006). These studies support the clinical trial to be conducted in this project. The overall aim of this project is to proved information that will advance the development of allopregnanolone as a treatment for field use to mitigate the effects of TBI in warfighters. In order to demonstrate the safety and efficacy of allopregnanolone for this application, a clinical trial will be conducted in the civilian setting. The main site for the trial is the UC Davis Medical Center, a Level 1 trauma center. At least 5 collaborating external sites will also enroll subjects. It is anticipated that 136 subjects will be enrolled. The study is designated as a phase 2, adaptive, two-stage, placebo controlled, double blind, randomized clinical trial. The primary objective is to determine in adults with moderate or severe TBI (GCS 3–12): (1) the safety of intravenous allopregnanolone compared to placebo during a 5-day continuous infusion starting within 8 hours after the injury; and (2) the efficacy of intravenous allopregnanolone treatment to improve GOS-E at 3 months after injury. Secondary objectives are to determine the clinical benefit of allopregnanolone treatment as assessed through secondary endpoints including mortality, GOS-E at 1 and 6 months, quality of life, global neurobehavioral function, depression, and late post-traumatic epilepsy. Allopregnanolone, the active pharmaceutical ingredient (API), has been manufactured for this trial according to Good Manufacturing Practices (GMP) standards mandated by the U.S. Food and Drug Administration (FDA). Intravenous product solutions have been developed by the UC Davis Good Manufacturing Practice Laboratory. There are 3 dosing levels: (1) placebo, (2) low (50 nM steady-state target level), and (3) high (150 nM steady-state target level). Within 8 hours after the injury, either placebo, low dose allopregnanolone, or high dose allopregnanolone is administered intravenously as a loading dose over 1 hour followed by a maintenance infusion. After 4 days, the maintenance dose is tapered by reducing the infusion rate to 75%, 50%, and 25% every 8 hours. Allocation of subjects among the doses is determined by an innovative adaptive trial design. The study is proceeding in two stages. The goal of Stage 1 is to assess product safety and confirm that the dosing regimen achieves the desired steady-state target serum concentrations of 50 nM (low) and 150 nM (high). The sample size of Stage 1 is flexible and enrollment in this stage will be considered complete when there is sufficient evidence that the low and high doses are safe and that the doses achieve the target steady-state concentrations. Data obtained from each Stage 1 study subject will be submitted to the Data Safety Monitoring Board (DSMB). The DSMB will decide when to proceed to Stage 2. Stage 2 utilizes adaptive allocation to the low and high dose to determine the relative efficacy of each dose and if allopregnanolone is superior to a placebo.

The primary outcome measure of the trial is the Glasgow Outcome Scale–Extended (GOS-E). The study is designed to detect a 1 point improvement. A 1 point improvement is clinically significant as such an improvement would place the GOS-E at the level reported for patients with mild TBI (GCS 13–15) (Hudak et al., 2005). Several authors have found that

greater disability and handicap as measured by the GOS and GOS-E are associated with subjective self-reports of poorer outcome. Specifically, individuals with poorer outcome as measured by the GOS or GOS-E had a higher frequency of depressive symptomatology (McCleary et al., 1998; Wilson et al., 2000). Poor outcome is also associated with reduced mental well-being and problems in neurobehavioral functioning (Wilson et al., 2000). Overall, the improved outcome contemplated by allopregnanolone treatment is expected not only to be associated with improved neurological function but also with an improved subjective sense of satisfaction with life (Wilson et al., 2000). Since it is difficult to conduct clinical research in a war zone, we have chosen to conduct this research in a civilian setting. Nevertheless, we believe that the results obtained will be applicable to the use of allopregnanolone in a military situation. Such application has the potential to have a dramatically positive impact on the function, wellness, and overall quality of life for military Service members affected by TBI. Caregivers and families will also be positively impacted since affected Service members with less disability will require less demanding care. The Brain Injury Association of America estimates that the long-term cost of care for a person with severe TBI is $4.1 to 9 million. Such an individual may require 5 to 10 years of rehabilitation and follow-up services. Therefore, in addition to providing improved function, well-being and overall quality of life, the improvement contemplated by allopregnanolone treatment should result in substantial societal cost savings.

Section II – Body

Summary of progress. Allopregnanolone has not previously been administered to humans for the treatment of any disease and it is not approved by the FDA for human use. Prior to enrolling subjects in the clinical study it was necessary to manufacture and test allopregnanolone API according to FDA-mandated GMP requirements, to create allopregnanolone intravenous formulations, to select a compatible container for the formulations, and assure product stability. Description of the progress made on these tasks was provided in previous annual reports.

At the same time as the product forms for the clinical trial were being developed, we created a protocol for the clinical trial and we constituted a team of clinicians and scientists at UC Davis with the diverse skills required to conduct the clinical trial. We also developed a charter for the Data Safety Monitoring Board (DSMB) and recruited the members of this committee. A site operations manual was also developed.

Also as described in previous annual reports, following a meeting with the FDA Division of Neurology Products we prepared and filed an IND, which was approved on May 7, 2012. The IND gave us authorization to administer our drug product formulations in the setting of an investigational trial. We received specific guidance from the FDA regarding the requirements for our clinical trial. Among the many requirements imposed by the FDA was the requirement that we carefully monitor blood plasma levels of allopregnanolone during the conduct of the trial to insure that dosing does not exceed limits mandated by the FDA. In addition, the FDA recommended that we examine more than one dose. In order to meet these requirements, we developed a bioanalytical method for the measurement of allopregnanolone in human blood plasma that utilizes an ultrahigh pressure liquid chromatograph (UPLC) system and tandem quadrapole mass spectrometer (MS/MS). To meet the FDA requirement that we examine more than one dose, we developed an innovative adaptive clinical trial design with assistance from Berry Consultants, who will provide ongoing assistance during the course of the trial. We also developed a statistical analysis scheme in consultation with statisticians at UC Davis. A case

report system was designed and, in consultation with the UC Davis Clinical and Translational Research Center (CTSC), we designed a database for the secure collection of data from the clinical trial using REDCap (Research Electronic Data Capture). In order to meet the sophisticated requirements of the adaptive trial design, we contracted with Bracket for the development of an interactive web response system to monitor drug supply and carry out randomization. In the course of communication with the FDA through the submission of an IND document and several requests for information, our IND

In addition, we submitted our trial for approval to the UC Davis Institutional Review Board (IRB), ultimately receiving authorization to begin the trial on May 11, 2012. With the approval from the FDA and IRB in hand, we were able to receive approval from the Human Research Protection Office (HRPO) on July 18, 2012. We published the clinical trial on ClinicalTrials.gov. We also enlisted the UC Davis Investigation Drug Services Pharmacy to develop methods for storage and dispensing of the drug product forms. In conjunction with Bracket, a division of United BioSource Corporation, an interactive web response system (IWRS) was built. The IWRS is a web-based system for patient randomization, patient deactivation, GOS-E score recording, drug dispensation, drug shipment receipt, tracking of lost or damaged IV bag, and unblinding. The system provides web reports essential to study management and inventory control.

The study was opened for enrollment on May 17, 2013. [As of December 16, 2013, a total of 11 subjects had been enrolled.] Each enrolled subject was treated according to the study protocol. No adverse events related to the study drug were reported. The study team is monitoring UC Davis Medical Center on an around-the-clock basis to ensure that any eligible patient with traumatic brain injury is provided an opportunity to participate in the study. We do not believe that any such patients have escaped attention. Several subjects were not enrolled, as they did not meet inclusion criteria.

Provisions to Recruit Additional Study Sites. In order to accelerate completion of the study, we plan to recruit at least 5 additional study sites. We have had discussions with many potential sites and the following institutions have indicated an interest in collaborating with us on the project: University of California, San Francisco; University of California, San Diego; University of Colorado; Barrow Neurological Institute; University of Southern California; University of Iowa. We have received local IRB approval to enlist external sites and the external sites have begun the process of obtaining approval from their own IRBs and from HRPO. Patient enrollment and treatment will be conducted at the external sites according to the same protocol as used at UC Davis Medical Center. Our study team will monitor study conduct at the external sites to ensure rigorous compliance with study requirement and reporting.

Revision of Statement of Work (SOW) and Budget. A revised budget and SOW was submitted in early September 2012 and a revised grant award was received on March 15, 2013. We are finalizing a further revision of the SOW and budget to account for the external sites.

Section III – Key Research Accomplishments

- Actively recruiting subjects.
- No adverse safety signals in subjects treated to date.

- Outcome data being collected.
- Finalizing contracts with external sites to accelerate recruitment.

Section IV – Reportable Outcome

None.

Section V – Conclusion

This project seeks to provide initial data on the safety and effectiveness of allopregnanolone in improving neurobehavioral outcome and reducing mortality in adults with moderate to severe TBI through a two-stage, adaptive, placebo-controlled, double blind, randomized clinical trial. During year 1, we located a manufacturer for the API (allopregnanolone) and began manufacturing. We also undertook extensive development work on the clinical trial protocol. During year 2, we finalized API manufacturing, primarily focusing on assessment of chemical purity and stability. We also created product formulations and assembled the large base of information required for IND filing. We met with the FDA in a Pre-IND meeting and in response to the agency's comments we modified our protocol to meet the requirements defined by the agency. We developed a novel adaptive trial design that provides a means to meet the FDA requirements regarding pharmacokinetics and allows us to address FDA guidance to assess more than one dose. Using the protocol and an extensive base of information on allopregnanolone, an IND package was developed and submitted to the FDA. We also submitted our protocol for review by our local IRB and to HRPO. During year 3, our IND was approved. We also received IRB and HRPO approval. Under the terms of our clinical study award, HRPO approval was required for payments to be made after the first year of the award. Therefore, no funding beyond the first year allocation was received. The unavailability of funding substantially slowed our progress during year 3. Because of the altered timeline and also key changes in the study because of requirements mandated by the FDA, at the time we obtained HRPO approval, a major budget revision was required. This occupied our attention beginning in August 2012 and continued until the revised grant award was received on March 15, 2013. Resumption of funding allowed us to rapidly begin subject enrollment. We have successfully enrolled subjects, who have been randomized to receive placebo or low dose allopregnanolone (50 nM target plasma concentration). We expect to shortly complete enrollment of the initial group of subjects (6 low dose allopregnanolone and 6 placebo). We are making plans for a meeting of the DSMB upon completion of these enrollments. The DSMB will review the safety information from these subjects and make a decision as to whether it is safe to randomize some subjects to high (150 nM target plasma concentration) dose allopregnonlone. Given the lack of safety signals to date, we anticipate that it will be possible to progress to the high dose.

In sum, the research conducted to date under this award has advanced the development of a potential treatment approach for adults with moderate and severe TBI. While there were many challenges and uncertainties in the program, all barriers to progress were successfully overcome. We are actively recruiting subjects at UC Davis Medical Center. In order to accelerate recruitment, we are enlisting external sites and expect to have 5 or more such sites operational shortly.

Our research and development activities provide many beneficial spin-offs apart from the conduct of the clinical study itself. The novel methods we have developed for the GMP manufacturing of pharmaceutical grade allopregnanolone and the production of intravenous product formulations can be applied by others who seek to investigate allopregnanolone in clinical trials for the treatment of TBI or other conditions. The methods are also applicable to the eventual production of allopregnanolone for deployment as a treatment agent if approved for use by regulatory authorities. Our approved IND defines the regulatory requirements for allopregnanolone product forms and for the clinical study of allopregnanolone. Our activities under this award have led to the creation of allopregnanolone product forms that are FDA approved for investigational use. In addition, the novel clinical trial design we have developed could also be adapted by other researchers seeking to study allopregnanolone or other agents in the treatment of TBI.

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